

Gestational Diabetes Mellitus: A Comprehensive Analysis of Risk Determinants and Consequences

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ABSTRACT

Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy. During pregnancy hyperglycemic condition develops that affects the mother and offspring. The complications of pregnancy and the prevalence of undiagnosed hyperglycemia in young women are increasing concern for maternal health. The etiology of GDM is complex, associated with genetic and environmental factors. The symptoms of GDM are frequent urination, blurred vision, dry mouth, thirst, fatigue, etc. GDM is mainly type 2 diabetes mellitus, the inability of beta cells of the pancreas to release insulin, and pregnancy hormones are also responsible for the insulin resistance pathway which is created by type 2 diabetes mellitus in pregnant women. The GDM diagnosis is achieved using the glucose challenge test (GCT) and oral glucose tolerance test (OGTT). Dietary modifications and physical activity are the primary treatments for GDM, but oral hypoglycemic agents, metformin, and glyburide are usually used in India and other countries. GDM increases the risk of short-term and long-term complications, including obesity, overweight, impaired glucose metabolism, and cardiovascular diseases, in both mother and infant. Monitoring of the development of offspring and recommendation of a healthy lifestyle for the children and family is recommended.

Keywords: Insulin, Diabetes mellitus, GDM, Plant, Drug

INTRODUCTION

For years, researchers have studied the impacts of diabetes, a fatal disease that causes symptoms such as extreme thirst, and frequent urination. The Indian physician Sushruta in 400 B.C. described the sweet urine of affected individuals and recognized it as the 1st sign of diabetes termed glucosuria. The term "diabetes" was originally used around 250 B.C. Thomas Willis invented the full phrase "diabetes mellitus" in 1674^[1]. Diabetes treatments were incredibly varied

until the middle of the 1800s. Insulin was used to treat the first diabetic patient in 1922. In 1923, Banting and Macloed were awarded the Nobel Prize for the discovery of insulin ^[2]. A revolution came with the production of recombinant human DNA insulin in 1978. New human insulin was created rather than using animal insulin. The insulin-making cells of our body are known as beta cells, present in the pancreas ^[3]. In 1958, Frederick Sanger was awarded his first Nobel Prize for determining the sequence of the amino acids that make up insulin ^[4].

Diabetes Mellitus

Diabetes Mellitus is a serious disease that occurs when the pancreatic beta cells are unable to synthesize insulin hormone, resulting the blood sugar level became high. This is a metabolic disease that is characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both. Diabetes is mainly characterized by the inability of pancreatic beta cells to release insulin hormones, which help to maintain the level of glucose ^[5]. Obesity, bad diet, physical inactivity, family history of diabetes, aging, and poor nutrition during pregnancy, are all risk factors for type 2 diabetes mellitus. Diabetes mellitus leads to reduced quality of life, and a greater risk of heart disease, renal disease, stroke, blindness, and peripheral neuropathy ^[6]. According to estimates by WHO and the International Diabetes Federation, there are currently 463 million people worldwide who have diabetes; by 2030, that number is expected to rise to 578 million, and by 2045, it will reach 700 million. Globally, as well as, especially in India, the number of people being diagnosed with diabetes is rising. It was predicted that there would be 69.9 million new cases of diabetes by 2025. Most of the cases are due to diabetes detected before pregnancy (they are affected by type 1 diabetes or type 2 diabetes). Three types of diabetes occur such as Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), and Gestational diabetes mellitus (GDM).

Type 1 diabetes mellitus, is the autoimmunological trigger that leads to the destruction of beta-cells in the pancreas and leads to loss of insulin secretion ^[7]. This condition is also known as juvenile diabetes. Type 1 begins at a young age, and is largely inherited. Beta cells of the pancreas do not secrete the optimum level of insulin due to which blood glucose levels are higher ^[8]. Treatment includes administration of insulin injections to the patient this is also known as insulin-dependent diabetes.

Type 2 diabetes mellitus is the most common metabolic disorder associated with obesity and leads to insulin resistance. In this, there is a decline in insulin secretion by beta-cells of the pancreas and the inability of tissue to respond properly to insulin ^[7,9]. This is also called adult-onset diabetes, as occurred in adult age. Treatment includes the drug Metformin which increases the level of glucose in the cells and transfers into the liver, and also increases glycogen production, also other glucose-lowering agents required for treatment ^[10].

Gestational diabetes mellitus (GDM) is caused by type 2 diabetes mellitus. Glucagon is the main hormone opposing the action of insulin and is released when food is scarce. Whereas insulin triggers the formation of glycogen (an energy-requiring process, or anabolic effect), glucagon triggers glycogen breakdown, which releases energy (a catabolic effect). In the absence of glucose, body uses fat and proteins as the energy source. The Blood glucose levels do not remain constant, they rise and fall depending on the body's needs and are regulated by hormones ^[11].

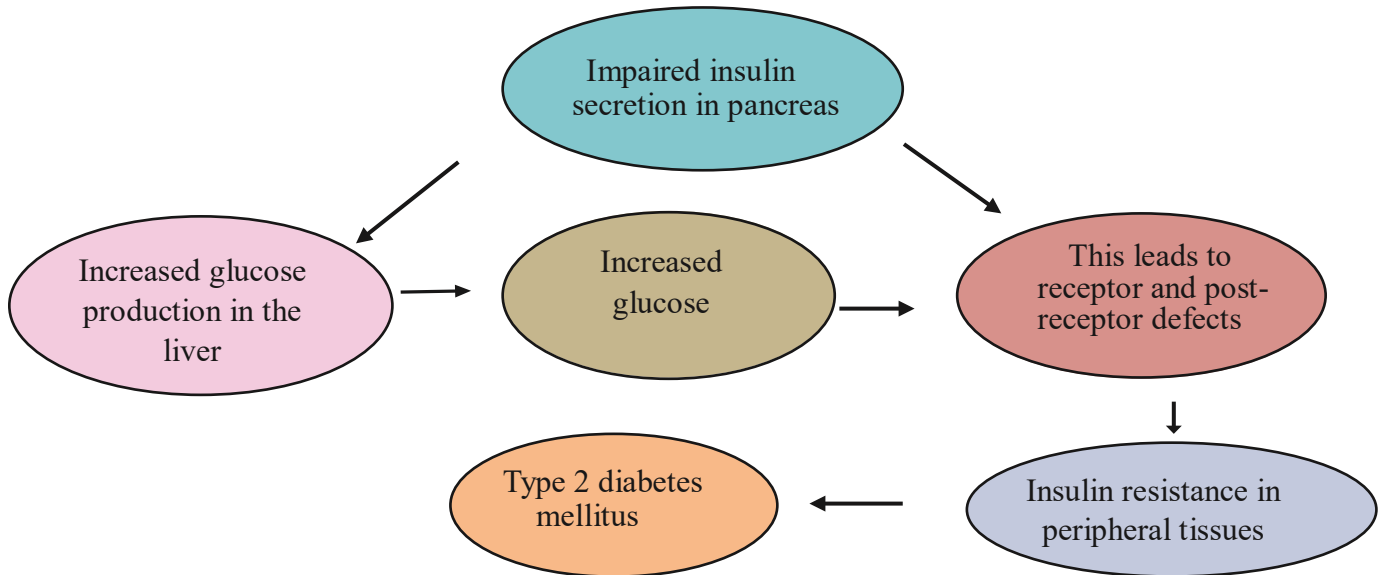


Figure1. Role of insulin in type 2 Diabetes Mellitus

Gestational Diabetes Mellitus

A rise in blood glucose levels during pregnancy is a sign of a condition known as gestational diabetes mellitus (GDM). This can be due to environmental and genetic factors such as Age, hypertension, weight, smoking, drug abuse, previous miscarriage, multiple pregnancies, malnutrition, stress and anxiety, genes, environmental effects, lifestyle, etc. [12]. Some more factors associated with GDM are overweight before the person gets pregnant, blood sugar levels are higher than normal, polycystic ovary syndrome (PCOS), high blood pressure, high cholesterol, heart disease or other medical complications, and miscarriage, among others [13,14]. The weight gain in pregnancy is due to more release of adipokines from adipose tissues and the adipokines resistance, which also increases intra-myocellular lipids and increases cellular oxidative stress with the generation of reactive oxygen species. During pregnancy, the placenta synthesizes hormones that increase glucose in the body for normal functioning, and the pancreas releases insulin to maintain the blood glucose level [15]. But in gestational diabetes mellitus beta cells are unable to synthesize enough insulin. There are two hormones Human placental lactogen (hPL) and hPGH (human placental growth hormone) increase up to 30-folds and 6-8-folds, respectively, throughout pregnancy and induce insulin releases from the pancreas in pregnancy. The hPL can lead to peripheral insulin resistance and hPGH replace the normal pituitary growth hormone. Insulin is primarily affected by high levels of pituitary growth hormone [16].

In normal situations, the Insulin binds to its receptor, and become dimerize. When insulin binds to the insulin receptor, the receptor's adaptor protein, known as IRS-1 (insulin receptor substrate-1) and IRS-2 (insulin receptor substrate-2), tyrosine (an amino acid involved in the synthesis of insulin) gets phosphorylated; IRS-1 binds to the inner cell of the insulin receptor and IRS-1 gets phosphorylation. IRS-1 binds to the p85 alpha subunit of PI3 kinase (phosphatidylinositol 3-kinases). This PI3K gets phosphorylated and converted the PIP2 (Phosphatidylinositol

4,5bisphosphate) into PIP3 by kinase activity. PIP2 is a membrane-bound protein present in the cytoplasm [17]. After that, PIP3 activates AKT, a Protein kinase B (PKB), which is the collective name of a set of three serine/threonine specific protein kinases that play key roles in processes such as metabolism of glucose, cell proliferation and apoptosis, transcription, and cell migration etc [17]. AKT also plays role in transfer of GLUT 4 transporter from the cytoplasm to the cell membrane then GLUT 4 absorbs the glucose. In the normal state, GLUT4 is present in the cytoplasm of the cell, after the binding of insulin to its receptor, it translocates on the membrane. As a result, glucose enters the inner cell and is used as an energy source [18].

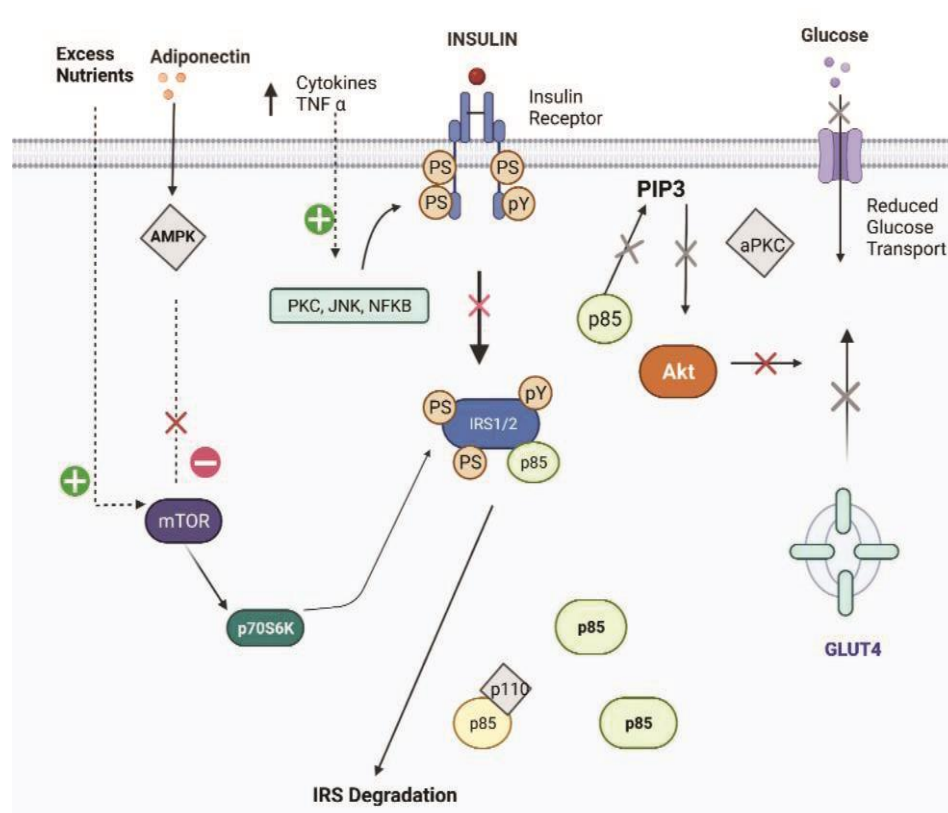


Figure 2. Insulin Resistance Signaling Pathway. IRS-1: insulin receptor substate-1, PIP3: phosphatidylinositol 3-kinases, PIP2: Phosphatidylinositol 4,5bisphosphate, PKC: phosphokinase c, JNK: Jun N-terminal kinase, NFkB: nuclear factor kappa B cells, mTOR 1: mammalian target of rapamycin 1, AMPK: AMP-activated protein kinase, GLUT 4: Glucose transporter type 4, TNF α : tumor necrosis factor α

In GDM patients, the insulin binds to the insulin receptor and they form dimerization. After that, the serine gets phosphorylated rather than tyrosine. Phosphorylation of IRS-1 occurs on serine residue rather than tyrosine. This results in the activation of JNK, PKC, NF-kB, and TNF alpha pathways. The entire pathway has been turned on. The IRS has been downgraded, and they are unable to assist with the GLUT 4 transfer. This pathway occurs in GDM patients as shown in (Figure 2) [19].

Some other factors also play an important role in the pathogenesis of insulin resistance:

Adiponectin consists of 244 amino acids and has a domain structure. Adiponectin is an important regulation of glucose homeostasis and insulin sensitivity, and several reports confirm an inverse relationship between insulin resistance and plasma adiponectin levels. The level of adiponectin decreases in early pregnancy and is inversely related to maternal BMI and insulin sensitivity ^[20].

Leptin is a 16kda protein hormone, which plays an important role in regulating energy intake and is one of the best-known hormones for obesity in humans. During pregnancy, leptin is produced by placental cells. The reduction of insulin secretion from pancreatic beta cells is due to the effect of leptin on the ATP-sensitive potassium channels. Leptins prevent beta cell stimulation by blocking the cAMP signaling pathway. It may hinder insulin secretion through cAMP- dependent protein kinase A (PKA) or protein kinase C (PKC). The level of leptin is increased in GDM patients. More than 90% of placental leptin is released in the maternal phase. Leptin also helps in embryonic implantation, human fetus development, developing growth, and organogenesis. Additionally, it increases the production of TNF- and IL-6 by monocytes, which causes inflammation and promotes insulin resistance ^[21].

Clinical symptoms of Diabetes in pregnant women

GDM symptoms include 3P i.e. Polydipsia (increased thirst), Polyphagia (increased hunger), and Polyuria (increased urination), others are unplanned weight loss, weakness, tiredness, fatigue, dry mouth, slow healing sores or cuts, and blurred vision.

Clinical intervention to manage diabetes mellitus in pregnant women

Certain lifestyle habits help in managing diabetes which include

- Dietary changes

Fruits have a low glycemic index (GI), which can help control blood sugar levels. Certain fruits, vegetables, and vitamins are good for GDM patients such as blackberries, strawberries, tomatoes, oranges, spinach, carrots, broccoli, cauliflower, cucumbers, cashews, and almonds ^[6].

- Active lifestyle and practices

Natural and holistic healthcare is popular in India, and there is some limited evidence that medicinal herbs like ashwagandha and traditional exercise like yoga may help lower glucose levels. Higher-intensity exercises can help too. A study showed that vaman dhauti practice (emetic therapy) caused a reduction in fasting and blood sugar levels ^[22,23,24]. It is believed to increase glucose uptake, minimize insulin resistance, and promote the function of insulin by reducing levels of circulating free fatty acids in the body. The abdominal pressure created during kapalbhati improves the efficiency of β -cells in the pancreas. Shankhprakashalana, is the process of cleansing the intestinal tract by practicing a set of yoga postures and drinking lukewarm water with salt in between ^[23]. The level of blood glucose falls significantly with this intestinal cleansing process. It has been claimed that this practice increases insulin

production and helps in the control of diabetes [25]. However, more studies are required to scientifically validate the outcome on clinical and molecular parameters.

Diagnosis and treatment of GDM

The two tests that are used for the diagnosis of GDM are the glucose challenge test and the oral glucose tolerance test. The screening of GDM takes place during routine prenatal care. The 24th and 28th weeks of pregnancy are determined by the screening test [26].

The screening test for DM mainly included-

1. Initial glucose challenge test: the first step to diagnosing gestational diabetes, fasting is not required. It is a type of blood test, in this test, patients take a glucose solution before 1 hour and the level of blood sugar is 190 mg/dl or more indicating gestational diabetes.
2. Oral glucose tolerance test: this test is like the initial glucose challenge test, except the initial sweet solution will have more glucose, and the sugar test is done every three hours and a fasting state before the test is taken up.

An average fasting glucose level is normally between 80 and 90 mg/dl and after a meal blood sugar level can increase to 120 to 140 mg/dl. If the random blood glucose value is greater than 200 mg/dl and the fasting blood glucose value is greater than 126 mg/dl suspect diabetes [27].

GDM can be treated by using drugs like metformin and glyburide [28]. Metformin is used for diabetes mellitus; metformin reduces insulin resistance by suppressing the release of glucose by the liver. According to previous studies, those taking metformin during GDM have less weight than those that person who use insulin. After 2 years continued examination states that females treated with Metformin had less fat around their organs which can make them less prone to insulin resistance in the future. After these findings a hypothesis stated that babies who were exposed to Metformin at an early age can achieve long-term benefits, but more research should be carried out on these lines to draw more affirmations. Other treatments and management include changes in dietary patterns and some physical activity in daily life schedules, which reduces the amount of glucose in the blood [29]. Some plants have been reported useful in the management of sugar levels in the blood, which along with dietary and lifestyle precautions may help in GDM.

1. *Acacia arabica* (Babul): The plant extract functions as an anti-diabetic medication by functioning as a secretagogue to release insulin. It has been reported that alloxanized rats are not affected by hypoglycemia compared to control rats [30]. In another study, powdered *Acacia arabica* was given to normal rabbits (2,3 and 4 g/kg body weight), and induced hypoglycemia was observed as insulin was released from pancreatic beta cells [31].
2. *Allium sativum* (Garlic): Allicin, a sulfur-containing chemical that has been demonstrated to have significant hypoglycemic action [32,33]. Increased hepatic metabolism, increased insulin release from pancreatic beta cells, and/or an insulin-sparing action are suggested to be the causes of this impact [34]. In comparison to sugar controls,

aqueous homogenate of garlic delivered orally to sucrose-fed rabbits boosted hepatic glycogen and free amino acid content, decreased fasting blood glucose, and lowered triglyceride levels in serum [35]. S-allyl cysteine sulfoxide (SACS), a Sulphur-containing amino acid that inhibits lipid peroxidation better than glipalamide and insulin, is the precursor of allicin and garlic oil. SACS was also reported to increase insulin production in beta cells isolated from normal rats in vitro [36].

3. *Azadirachta indica* (Neem): Hydroalcoholic extracts of this plant showed an anti-hyperglycemic effect in streptozotocin-treated rats, which was related to an increase in glucose absorption and glycogen deposition in isolated rat hemidiaphragm [37]. In addition to its anti-diabetic benefits, the plant has antibacterial, antimalarial, antifertility, hepatoprotective, and antioxidant characteristics [38].
4. *Eugenia jambolana* (Indian gooseberry, Jamun): In India, a decoction of *Eugenia jambolana* kernels is used as a home treatment for diabetes. Many herbal diabetic treatments contain this as a key ingredient. Aqueous and alcoholic extracts and lyophilized powder have antihyperglycemic effects [35]. The extract of jamun pulp showed a hypoglycemic effect within 30 minutes of injection in streptozotocin-induced diabetic rats, while the seed of the same fruit took 24 hours. When the extract was given orally to diabetic rats, blood insulin levels increased [39]. Insulin secretion was enhanced when plant extract was incubated with isolated Langerhans islets from normal and diabetic rats. These extracts likewise decreased the activity of insulin in the liver and kidney [40].

CONCLUSIONS

GDM (gestational diabetes mellitus) is a kind of diabetes that can impact both the mother and fetus as pregnancy hormones are affected, which causes peripheral insulin resistance. Insulin resistance in normal pregnancy is multifactorial, comprising decreased insulin's ability to phosphorylate the insulin receptor, decreased expression of insulin receptor substrate-1, and higher levels of the PI-3 kinase subunit p85. In GDM, the reciprocal and inverse changes in the degree of serine and tyrosine phosphorylation of insulin receptor and IRS-1, inhibit the signaling of GLUT4 translocation and glucose uptake. TNF- α and P70S6K1 levels were higher in GDM women. Insulin is typically the first line choice, which is followed by metformin and glyburide. These both maintain blood sugar concentrations for 1 or 2 hours but these may lead to some side effects such as nausea, vomiting, dizziness, upset stomach, etc. so, there is a need for alternative options of plant-based natural drugs which are also safe for pregnant women and shows potential result in gestational diabetes mellitus (GDM).

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